Patients With Hepatorenal Syndrome Should Be Dialyzed?

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Decompensated cirrhosis is an ominous medical condition that often places healthcare providers at a quandary of managing very complex clinical scenarios. The complexity of those scenarios further escalates when acute kidney injury (AKI) superimposes over decompensated cirrhosis, signifying the collision of two life-threatening disorders. Arguably, the difficulty of managing the coexistence of decompensated cirrhosis and AKI reaches its peak when the medical-decision making conundrum around the provision of dialysis is faced, particularly when the etiology of AKI is presumed to be hepatorenal syndrome type 1 (HRS-1).

HRS-1 is a unique form of AKI in patients with cirrhosis and portal hypertension mainly characterized by a profound reduction in kidney perfusion\(^1, 2\). The cornerstone of treatment of HRS-1 is vasoconstrictor therapy. However, vasoconstrictor therapy may only lead to improvement in kidney function in up to about 30 - 40% of the times\(^3\). Thus, patients with HRS-1 often rapidly deteriorate and reach a point when dialysis becomes medically necessary. Then, the traditional view has been that HRS-1 is associated with a uniquely high mortality rate\(^4-7\). In the absence of liver transplantation, its in-hospital mortality rate was reported to be around 90% and not affected by dialysis and with a median survival of 2 weeks\(^5, 6\). As a result, because of its presumed inability to extend survival, dialysis in such setting has been historically deemed futile.

*Is the evidence that the mortality of HRS-1 that progressed to need for dialysis is worse than that of any other cause of AKI unequivocal?*

The assertion that the mortality rate associated with HRS-1 is greater than that of other causes of AKI in cirrhosis originated from a report on 463 patients with cirrhosis and kidney failure\(^4\). The reported 90-day survival rate of 201 patients diagnosed with HRS-1 was 23% compared to 71% for those with a parenchymal cause of AKI. HRS-1 was linked to an odds ratio of 6.9 for 3-month mortality. The authors also reported a survival rate of 42% for hypovolemic AKI, surprisingly worse than that of parenchymal
AKI, a counterintuitive finding that raises concerns about proper adjudication of diagnoses. Importantly, the study did not report whether the survival rate differences among types of AKI were applicable to those requiring dialysis. Earlier studies limited to patients with cirrhosis who required dialysis reported dismal outcomes\textsuperscript{8,9}. Among 25 patients with cirrhosis and AKI requiring dialysis, the in-hospital mortality rate was 100\%\textsuperscript{9}. However, the cohort included 10 patients with HRS-1 and 11 with acute tubular necrosis (ATN) and fatalities occurred in both subgroups. Furthermore, most patients in that study were treated with peritoneal dialysis rather than hemodialysis. Therefore, the observations may not be fully applicable to current practice that is heavily leaned toward hemodialysis and continuous renal replacement therapy (CRRT). Nevertheless, a more recent European study demonstrated that among cirrhotics, AKI requiring dialysis (intermittent hemodialysis or CRRT) was associated with 91\% 90-day mortality compared to 43\% for AKI not requiring dialysis\textsuperscript{10}. However, no distinction was made based on cause of AKI.

A more recent study has further challenged the notion of worse outcomes of HRS-1 compared to ATN when the AKI state reaches the point of dialysis requirement. In a large cohort of 472 patients with cirrhosis and AKI who underwent dialysis, the mortality rates of those with HRS-1 as a cause of AKI were compared to those with ATN\textsuperscript{11}. Among those not listed for liver transplantation, 47 of 56 (84\%) patients with HRS-1 and 242 of 285 (85\%) of those with ATN died within 6 months. In addition, for those listed for liver transplantation, 24 of 62 (39\%) patients with HRS-1 and 35 of 69 (52\%) patients with ATN died within 6 months. Therefore, the authors concluded that there was no clear evidence that HRS-1 is linked to greater mortality compared to that of ATN. A preliminary examination to this question in our single center has revealed similar findings\textsuperscript{12}. Consequently, the existing evidence puts in question earlier observations and traditional assertions. Notably, the observational nature of the aforementioned studies further hampers the ability do draw unequivocal conclusions.
Can the diagnosis of HRS-1 be made with certainty? And if so, can that certainty be carried over to make decisions around provision of dialysis?

If it is assumed that HRS-1 that progresses to necessitating dialysis has indeed distinctly greater mortality compared to ATN or other forms of AKI, it then becomes critical to correctly diagnose the cause of AKI in patients with decompensated cirrhosis. In order to accomplish it, the standard approach is to utilize the diagnostic criteria established by the International Club of Ascites. However, those criteria are not without pitfalls. Multiple confounding factors exist in real clinical scenarios when one tries to apply those criteria. Illustrating those pitfalls, an examination of documented discharge diagnosis codes revealed that a correct diagnosis of HRS-1 was only assigned to 27 of 46 (59%) of hospitalized patients with cirrhosis. Similarly, in a single center study, manual review of medical records determined that correct adjudication of HRS-1 as cause of AKI occurred in only 27 of 73 (37%) individuals with AKI and decompensated cirrhosis. Even in an attempt to employ computational diagnostic algorithms, 104 of 504 (21%) of patients were categorized as “maybe HRS-1” or “indeterminate”. Thus, given the uncertainty and the lack of gold standard test for diagnosis, it seems unwise to place much weight in the distinction between HRS-1 and ATN when it comes to serious end-of-life recommendations. At best, practitioners can only suspect that the cause of AKI may be HRS-1. This uncertainty should translate into and open-minded approach when it comes to provision of dialysis.

Is dialyzing a patient with cirrhosis not eligible for liver transplantation completely futile?

Patients with cirrhosis who require acute dialysis, particularly those in intensive care units, are very complex with at high risk of death. Because dialysis is not offered in many instances under the premise of futility, there is paucity of data assessing their outcomes. In a descriptive study of 107 patients with decompensated chronic liver disease and AKI, which included 27 patients with HRS-1 as a cause of AKI, the role of hemodialysis was examined. One-year survival rate for those who received acute...
hemodialysis was 28% compared to only 2% for those with AKI who were not dialyzed even though it was indicated. Patients who were not dialyzed were significantly older and with greater incidence of coma, whereas those who received hemodialysis had higher rates of sepsis. The impact of hemodialysis on survival was further examined in the subgroup of patients with HRS-1 revealing a similar survival advantage, with 7 of 16 (43%) who received hemodialysis remaining alive at 1 year compared to 1 of 9 (11%) of those who did not receive dialysis. The same study looked at risk factors for mortality. Among those who received hemodialysis, thrombocytopenia, malignancy and encephalopathy were identified as being associated with higher mortality rate, but not HRS-1 diagnosis\textsuperscript{16}. In another study assessing factors affecting mortality rate in patients with cirrhosis and HRS-1 undergoing hemodialysis, it was found that requirement of CRRT, mechanical ventilation and catecholamine support were strongly associated with greater death rates\textsuperscript{17}. A more recent study in patients with alcoholic liver disease also reported the use of vasopressors and CRRT as the strongest indicators of mortality in AKI requiring dialysis\textsuperscript{18}. Therefore, in that report, elements intrinsic to critical illness were better indicators of mortality compared to those specific to chronic liver disease or cause of AKI.

What are the collateral implications of life-sustaining measures in patients with decompensated cirrhosis ineligible for liver transplantation?

While cumulative data may point towards a paradigm shift toward reconsideration for offering dialysis to patients with cirrhosis and AKI due to HRS-1, close attention has to be paid to examining the overall implications of maintaining those patients alive without a path for liver transplantation. A short report of 4 patients of HRS-1 who received hemodialysis despite being ineligible for liver transplantation illustrated a wide range of length of survival of 5 to 65 weeks\textsuperscript{19}. However, the extended survival was closely associated with frequent hospitalizations and an average 33% of the time spent in this hospital. This phenomenon aligns with a growing number of hospitalizations among cirrhotic patients despite a
trend for decreased mortality in the United States between 2002 and 2010\textsuperscript{20}. Therefore, it is recommended to carefully weigh on the potential for reversibility of the AKI and on the morbidity associated with a short-lived extension of life span with dialysis in a patient with cirrhosis and AKI not eligible for liver transplantation.

\textit{What conclusions can be made?}

To summarize, in our practice, we face 3 general types of scenarios (Figure 1). First, patients who are listed for liver transplantation or quickly deemed eligible for liver transplantation. For them, there is no doubt that offering dialysis is a reasonable step to take. Second, patients who are in the process of being evaluated for liver transplantation but no clear statement has been made about eligibility. This group represents probably a great percentage. For them, it seems prudent to view them as having potential to benefit for liver transplantation. Therefore, one should lean towards offering them dialysis while a clearer disposition is established. Third, patients who have been deemed ineligible for liver transplantation. Typically, those are critically (chronically and acutely) ill patients with comorbidities who have been historically negated from receiving dialysis. I would advocate that for these patients, a thorough assessment of the overall clinical and social condition of the patient and potential risks and benefits associated with dialysis has to be made in a similar fashion that we may do so for patients who are critically ill with AKI and multiorgan dysfunction in intensive care units. Within this group, for those with AKI in the ICU on mechanical ventilation, vasopressor support, coma and/or dependence of CRRT without reasonable expectation for AKI reversibility, I would conclude that offering dialysis could be futile. But in the absence of those concrete elements, I would favor offering dialysis while consulting palliative care medicine and engaging in extensive discussions with the patient and/or patient’s family or support circle in order to understand the patient’s wishes and personal circumstances, explain that the maintenance of life by virtue of dialysis for additional weeks or months of their lives may not provide comfort and may be accompanied by poor quality of life and more pain and suffering. For many patients
and their families, extra days weeks or months of life can be very meaningful and allow them to get their personal affairs together and move on to closure and acceptance of this critical and difficult juncture in their lives. For others, prolonging the inevitable is not an option and they may be more inclined to seek hospice care and decline the dialysis path.

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References


FIGURE LEGEND

Figure 1 | Proposed algorithm to approach medical decision making regarding provision of dialysis in patients with cirrhosis and AKI. ATN, acute tubular necrosis; HRS-1, hepatorenal syndrome type 1; CRRT, continuous renal replacement therapy; ICU, intensive care unit.